Parallel Kinetic Resolution

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In a competition experiment where a 1:1 mixture of two substrates reacts simultaneously with a single reagent, the initial product ratio corresponds to the inherent selectivity **s** (the ratio of competing rate constants). However, product ratio decreases with percent conversion because there is a continuous increase in the relative concentration (and therefore, the relative rate of reaction) of the less reactive substrate as the faster-reacting substrate is consumed. The kinetic consequences are well-known for the special case where the substrates are two enantiomers competing for an enantioselective chiral reagent (simple kinetic resolution).[1−3] In principle, the slower reacting enantiomer can be recovered with very high ee, but only if conversion is sufficiently high to consume essentially all of the more reactive enantiomer. Depending on selectivity, this can drastically reduce the yield of the purified unreacted enantiomer. Furthermore, increased conversion can only decrease the ee of the product derived from the more reactive enantiomer, approaching 0% ee as conversion approaches 100%. Exceptional selectivity is required to obtain *both* slow and fast reacting enantiomers (recovered substrate and product, respectively) with high ee and the theoretical maximum 50% yield for each (for example, **s** = 200, 96% ee; **s** = 500, 98% ee).[1] Such selectivities are currently beyond reach for most nonenzymatic kinetic resolutions and for many of the lipase-esterase experiments.[2a,b]

We report a method to maximize ee as well as percent conversion using a simple technique that maintains the optimum 1:1 substrate ratio throughout a competition experiment. This conceptual variation requires the use of two selective reagents in parallel. Parallel reactions have been encountered previously using catalysts that may contain more than one enzyme[4a,b] or catalysts that convert each enantiomer to a different product.[4b−d] Thus, Brooks *et al.* reported that baker's yeast reduces one of the enantiomers of a β-keto ester to a chiral alcohol and induces decarboxylation of the other enantiomer to afford an achiral ketone.[4a] In this case, enzymatic selectivity in the pathway leading to the chiral alcohol is already high, and the occurrence of a parallel reaction from the other enantiomer leading to the achiral product has no special advantage for enantiomeric purity. However, Brooks *et al.* recognized the unique feature that distinct products are formed in the competing reactions. Mathematical treatments of relevant parallel reactions have appeared,[5] including kinetic models for hypothetical reactions

catalyzed by two moderately selective enzymes (Straathof *et al.*).[5a] The latter workers concluded that the time evolution of ee should improve in the parallel experiment, but they did not include the case where the products of each of the competing reactions are distinct. This situation has special advantages that have not been discussed previously. As shown below, competing parallel reactions that produce two different chiral products can give substantially improved ee values up to the theoretical yield limit (50% of each enantiomer). We have called this process parallel kinetic resolution (PKR).

Consider two chiral reagents Z_1 and Z_2 having similar but opposite selectivity toward the enantiomers *(R)*-E and *(S)*-E in a reaction of the racemic mixture to afford enantiomeric products *(R)*-P_1 and *(S)*-P_1 from Z_1 and a second set of enantiomeric products *(R)*-P_2 and *(S)*-P_2 from Z_2. Assume that the larger rate constant $k_{1(R)}$ (for reaction of *(R)*-E with Z_1) is equal to $k_{2(S)}$ (for reaction of *(S)*-E with Z_2) and that the smaller rate constant $k_{1(S)}$ is equal to $k_{2(R)}$. In this ideal case, the overall rates of conversion of *(R)*-E and *(S)*-E must be identical, and the 1:1 ratio of starting enantiomer concentrations [*(R)*-E] and [*(S)*-E] must be maintained throughout. Therefore, the ratios of all four possible products (enantiomer pairs *(R)*-P_1 and *(S)*-P_1; *(R)*-P_2 and *(S)*-P_2) will remain constant from >0% to 100% conversion. The enantiomeric purity of the products P_1 and P_2 can be predicted directly from the corresponding selectivities s_1 (equal to $k_{1(R)}/k_{1(S)}$) and s_2 (equal to $k_{2(S)}/k_{2(R)}$) at all times. Thus, a PKR experiment using two simultaneous reactions of complementary enantioselectivity with $s_1 = s_2 = 49$ (100% conversion) would be equivalent to a simple kinetic resolution with **s** = 200 at 50% conversion![1] Theoretically, both experiments would allow total recovery of each enantiomer with 96% ee.

One simple variation of PKR involves competing reactions where the reagents Z_1 and Z_2 are related as the quasienantiomers, defined as two molecules Z_1 and Z_2 containing similar stereogenic carbons **C**[a][b][c][d] for Z_1 and **C**[a][b][e][c] (opposite configuration) for Z_2 such that Z_1 and Z_2 would be true enantiomers if the substituents [e] and [d] were identical.[3b] In this case, the requirement for similar reaction rates and complementary enantioselectivities is relatively easy to satisfy.

The chiral DMAP-derived salt **3** (from **1** and trichloro-*tert*-butylchloroformate) has been shown to discriminate between enantiomers of 1-(1-naphthyl)ethanol with **s** = 42 for the *(S)*-enantiomer in an acyl transfer process.[6] A quasienantiomer of **1** was easily made by benzylation of the precursor *(S)*-alcohol with benzyl bromide to give ether **2**. It was more difficult to find a chloroformate that would react with **2** to give an acyl transfer agent having high enantioselectivity and also the ability to form easily separated products. Hindered chloroformates gave the most promising results, and fenchyl chloroformate afforded an *N*-alkoxycarbonylpyridinium salt **4** that was shown to have the desired properties (**s** = 41 for *(R)*-alcohol). Fenchyl chloroformate was chosen strictly for reasons of bulk and cost (fenchyl alcohol, $0.10/g). The fact that the alkyl group is chiral is probably irrelevant to selectivity.[7] This feature did simplify the preliminary product assay (de estimated by ^{1}H NMR), but a more precise hplc assay was required to determine the **s** values.

Salts **3** and **4** (1.1 mol equiv) were generated in separate flasks (CH$_2$Cl$_2$ solution), combined, and treated with MgBr$_2$ (2.25 mol

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Table 1. PKR Experiments Using **3** and **4** to Resolve **7**[a]

entry	Ar	**5:6**[b]	yield (**5**)	ee (**5**)[d]	yield (**6**)	ee (**6**)[d]
1	1-naphthyl	1.0:1.0	46% (49%)[c]	88%	49% (49%)[c]	95%
2	2-naphthyl	1.0:1.0	49% (49%)[c]	86%	43% (49%)[c]	93%
3	*o*-tolyl	1.13:1.0	46% (53%)[c]	83%	46% (47%)[c]	94%

[a] 0.56 mol equiv each of **3** and **4**, 2.25 mol equiv of MgBr$_2$, 3 mol equiv of Et$_3$N, 1 mol equiv if racemic ArCH(OH)CH$_3$ in CH$_2$Cl$_2$ at room temperature, 36 h. [b] NMR ratio of crude products. [c] Yield vs internal standard, NMR assay. [d] hplc assay; see Supporting Information.

equiv), Et$_3$N (3 mol equiv), and racemic 1-(1-naphthyl)ethanol (1 mol equiv). The reaction was allowed to proceed to >98% conversion (NMR detection limit), and the product mixture of **5a** and **6a** was then treated with Zn/HOAc to selectively cleave the trichlorobutyl protecting group.[8] The resulting mixture of alcohol *(S)*-**7a** and the mixed fenchyl carbonate **6a** was easily separated. If desired, the reusable quasienantiomers **1** and **2** could be recovered (ca. 90% combined yield after chromatographic separation).[9]

According to hplc assay using a chiral stationary phase (csp), *(S)*-**7a** was shown to have 88% ee (49% yield based on internal standard NMR assay; 46% isolated). The mixed carbonate **6a** was assayed using hplc and was determined to have 95% de (49% isolated yield). These findings are summarized in Table 1 (entry 1), along with similar results from two other racemic secondary alcohols. To place the results into perspective, we note that a simple kinetic resolution would have to operate at **s** >125 to allow 49% recovery of one enantiomer with 95% ee (or de). The 95% de value observed for **6a** is identical to that expected in the ideal PKR experiment with **s** = 41−42 and identical rates for both reagents. However, the 88% ee for **5a** indicates that in this case there is some interference from components of the competing parallel reaction. Otherwise, this value should also be ca. 95% ee. One possible explanation is that a small amount (ca. 3%) of "leakage" occurs from **4** to **8** in the course of the PKR experiment, but our assay was not sufficiently precise to rule out other possible explanations.

a Ar = 1-naphthyl
b Ar = 2-naphthyl
c Ar = *o*-tolyl
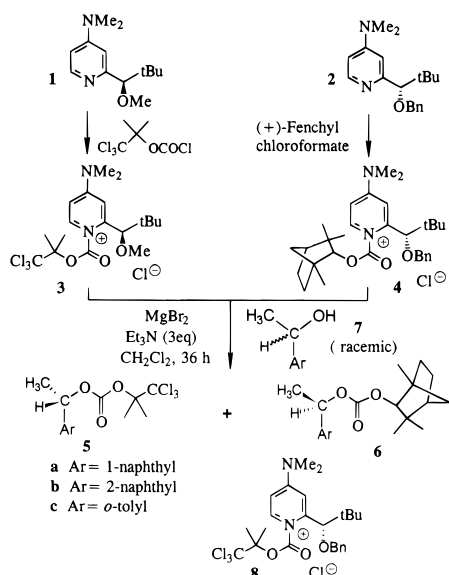
The above data confirm the feasibility of PKR. Products **5a** and **6a** and **5b** and **6b** were formed in a 1:1 ratio, indicating that nearly ideal relative rate conditions were achieved. This was desired to maintain the optimum 1:1 relative ratio of enantiomers throughout the conversion from the racemate to products. In the case of **5c** and **6c**, there was a measurable

deviation from the 1:1 ratio and a correspondingly larger difference in product ee values (entry 3), probably due in part to undesired competition from the "mismatched" alcohol enantiomer reacting with **3**.

Identical reactivities ($k_{1(R)} = k_{2(S)}$, etc.) in the competing reactions are desirable, but they are probably not obligatory. In principle, it should be sufficient to adjust the relative concentrations of [Z$_1$] and [Z$_2$] so that the parallel reactions occur with similar rates over most of the reaction coordinate. Furthermore, there is no need for the parallel reactions to involve similar functional group conversions, as in the examples illustrated here. All that is necessary is that the two competing reactions (1) occur without mutual interference, (2) have similar rates, (3) have complementary enantioselectivity, and (4) afford distinct products. This means that any two selective derivatizations of a chiral racemic substrate can be used as the competing reactions in the PKR experiment.[10]

In principle, one or both of the competing reactions can be catalytic, provided that each catalyst is selective for the reagent as well as for the substrate enantiomer. Enzymatic catalysts could be used, but this variation would be worthwhile only if the selectivity is below **s** = ca. 150. Otherwise, efficient enantiomer recovery is already possible without PKR. The PKR process would not be preferred in systems where dynamic kinetic resolution is possible or where the less reactive enantiomer can be recycled *in situ*.[11,12] These methods provide an alternative means for maintaining the optimal 1:1 ratio of enantiomers where necessary, and they have the advantage that both enantiomers are converted into a single product.

The W-tube "resolving machine" concept of Cram *et al*. (enantioselective transport) also depends on maintaining a 1:1 enantiomer ratio.[12] In this case, dilution-driven transport corresponds to the chemical derivatization component of PKR. Another PKR application is inherent in reactions where two enantiomers of a racemic substrate are selectively converted into separable, chiral products (regioisomers, diastereomers, etc.) by a *single* chiral reagent or catalyst. Some of the enantioselective Bayer−Villiger oxidations[4b,c] and diazoketone insertions[4d] reported previously belong to this category, and increased efficiency is expected under ideal PKR conditions (equal or similar rates; complementary enantiomer-dependent regioselectivity).

PKR is not restricted to the derivatization of enantiomers under *stoichiometric* conditions. However, this is one of the easier variations, and it provides sufficient advantages in selectivity and efficiency that the use of stoichiometric reagents in kinetic resolutions may need to be reevaluated in certain cases. Even a modest selectivity of **s** = 20 in the derivatization step could provide chiral products in 90% ee with near-total material recovery using PKR conditions.

Supporting Information Available: Preparation of **2**, fenchyl chloroformate, characterization of **6a,b,c**, and representative procedures for PKR (5 pages). See any current masthead page for ordering and Internet access instructions.

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(9) The true enantiomer of **1** could have been used in place of **2**, but this PKR experiment would racemize the chiral DMAP derivatives while it resolves the substrate enantiomers.

(10) In principle, mixtures of two achiral components (diastereomers; regioisomers; etc.) could also be derivatized with improved efficiency using two complementary reagents in parallel if they react selectively with each isomer to afford a distinct product.

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